ANSWER 1 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Claimed are buprenorphine monocarboxylates I [R = linear or branched (un)saturated aliphatic group optionally substituted with aryl, or aryl optionally substituted with linear or branched (un)saturated aliphatic group; with the proviso that R is not selected from Me, Et, Pr, Bu, pentyl, hexyl, CH(Me)2], and buprenorphine dicarboxylic acid diesters II [R1 = divalent group derived from (un)saturated aliphatic group optionally substituted with Ph], which exert a longer analgesic effect as compared with buprenorphine hydrochloride. Also claimed are the processes for preparation of I and II, and long-acting analgesic pharmaceutical compns. containing ≥1 selected from buprenorphine, I, and II and oily vehicles, and a method to bring analgesia by administering the compns. to animals or human. A composition containing II (R1 = sebacoyl), prepared from buprenorphine (HCl) and sebacoyl chloride, and sesame oil exhibited analgesic duration for 96 h at 0.3 μmol/kg i.m.

ACCESSION NUMBER: 2004:512395 CAPLUS
DOCUMENT NUMBER: 141:59722
TITLE: Buprenorphine monocarboxylic or dicarboxylic acid derivatives, their preparations, long-acting analgesic compositions containing them, and analgesia using them
INVENTOR(S): Wang, Jhi-Joung
PATENT ASSIGNEE(S): Chimei Hospital, Taiwan
SOURCE: Jpn. Kokai Tokkyo Koho, 86 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

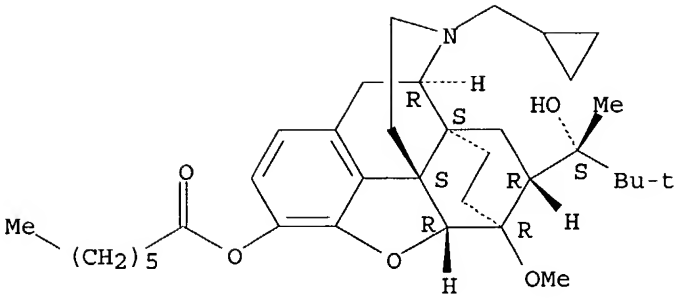
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2004175706	A2	20040624	JP 2002-342688	20021126

PRIORITY APPLN. INFO.: JP 2002-342688 20021126
OTHER SOURCE(S): MARPAT 141:59722

IT **171018-33-0P**, Buprenorphine enanthate **692729-06-9P**, Buprenorphine benzoate **693242-76-1P**, Buprenorphine decanoate **693242-77-2P**, Buprenorphine pivalate **693242-78-3P**, Buprenorphine palmitate **693242-79-4P**, Dibuprenorphine pimelate **693242-80-7P**, Dibuprenorphine sebacoyl ester
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of buprenorphine monocarboxylic or dicarboxylic acid esters and long-acting analgesic compns. containing them)

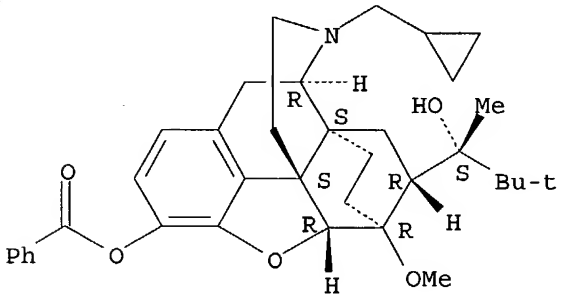
RN 171018-33-0 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-[(1-oxoheptyl)oxy]-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



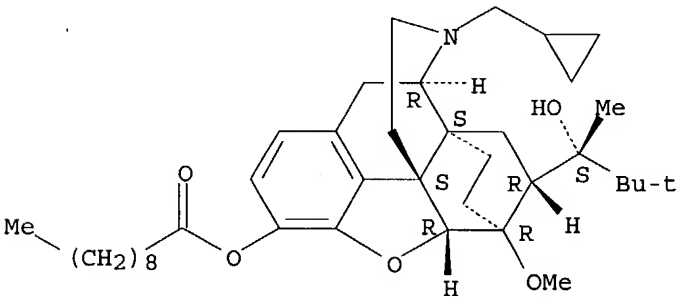
RN 692729-06-9 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 3-(benzoyloxy)-17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



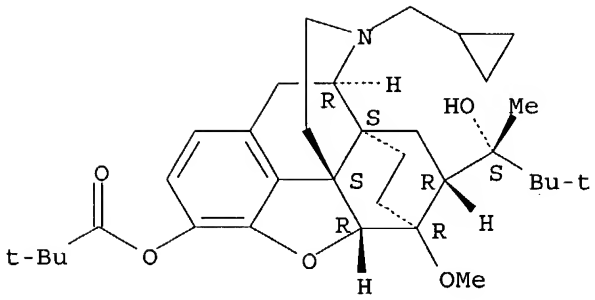
RN 693242-76-1 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-[(1-oxodecyl)oxy]-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



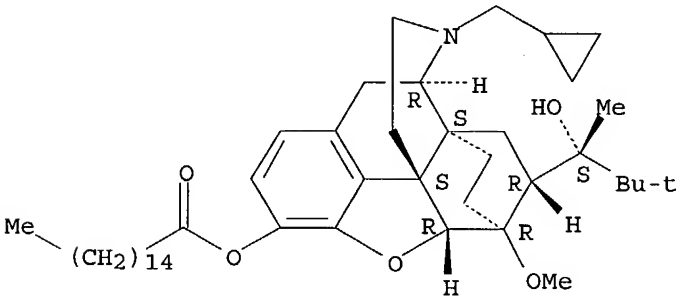
RN 693242-77-2 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-3-(2,2-dimethyl-1-oxopropoxy)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 693242-78-3 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-[(1-oxohexadecyl)oxy]-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

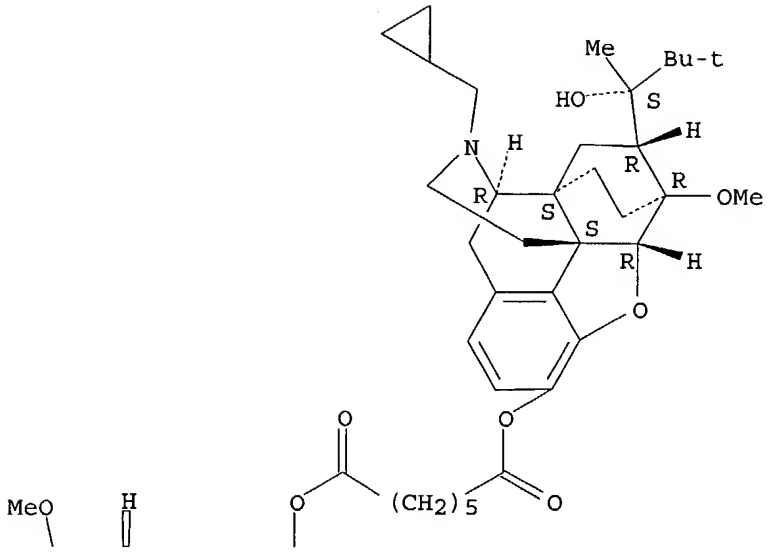
Absolute stereochemistry.



RN 693242-79-4 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 3,3'-[(1,7-dioxo-1,7-heptanediyl)bis(oxy)]bis[17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-, (αS,5α,7α)-(α'S,5'α,7'α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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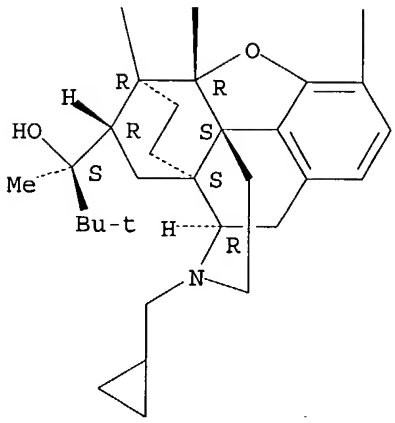
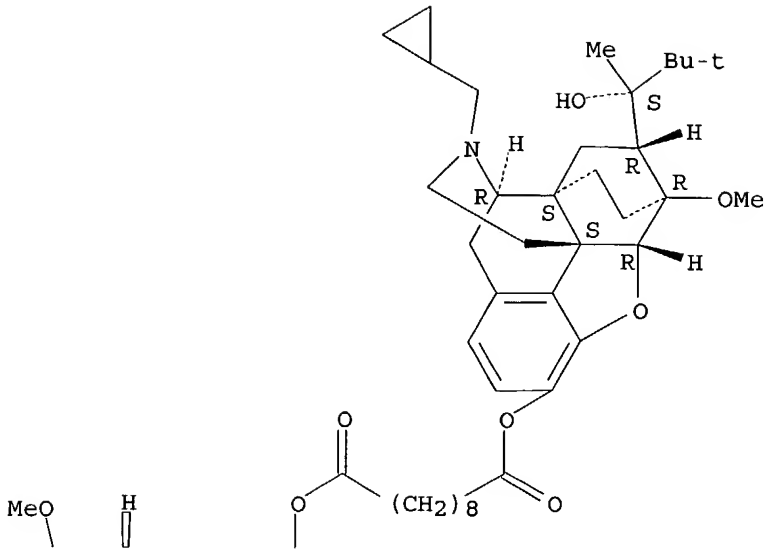


RN 693242-80-7 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 3,3'-[(1,10-dioxo-1,10-decanediyl)bis(oxy)]bis[17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-, (αS,5α,7α)-(α'S,5'α,7'α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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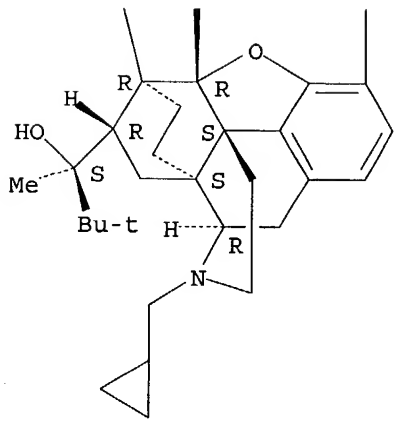

L4 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Disclosed herein are novel buprenorphine monocarboxylic ester derivs., such as I [R = straight-chain or branched saturated or unsatd. aliphatic group optionally substituted with an aryl group, or an aryl group optionally substituted with straight-chain or branched saturated or unsatd. aliphatic group;
with the proviso that R is not selected from Me, Et, (CH)2Me, (CH)3Me, (CH)4Me, (CH)5Me, CH(Me)2], and dibuprenorphine dicarboxylic ester

derivs., such as II [R1 = divalent moiety of a saturated or unsatd. aliphatic group optionally substituted with Ph group], which exert a longer analgesic effect as compared to buprenorphine hydrochloride. Also disclosed are the processes for synthesizing I and II, and long-acting analgesic pharmaceutical compns. containing a compound selected from buprenorphine base and the novel ester derivs. of buprenorphine. Thus, dibuprenorphine pimelate II [R1 = (CH2)5], prepared by the reaction of buprenorphine hydrochloride and pimelic dichloride, exhibited analgesic duration for 72 h at a dose of 0.3μM/kg.

ACCESSION NUMBER: 2004:427626 CAPLUS
DOCUMENT NUMBER: 140:423853
TITLE: Preparation and long acting analgesic pharmaceutical composition of ester derivs. of buprenorphine
INVENTOR(S): Wang, Jhi-joung
PATENT ASSIGNEE(S): Chi Mei Foundation Medical Center, Taiwan
SOURCE: Eur. Pat. Appl., 51 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

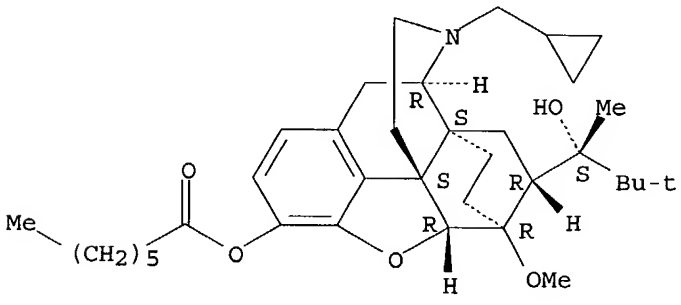
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1422230	A1	20040526	EP 2002-258083	20021125
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
PRIORITY APPLN. INFO.:			EP 2002-258083	20021125

OTHER SOURCE(S): MARPAT 140:423853

IT **171018-33-0P**, Buprenorphine enanthate **693242-76-1P**, Buprenorphine decanoate **693242-77-2P**, Buprenorphine pivalate **693242-78-3P**, Buprenorphine palmitate **693242-79-4P**, Dibuprenorphine pimelate **693242-80-7P**, Dibuprenorphine sebacoyl ester
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and analgesic pharmaceutical composition of ester derivs. of buprenorphine)

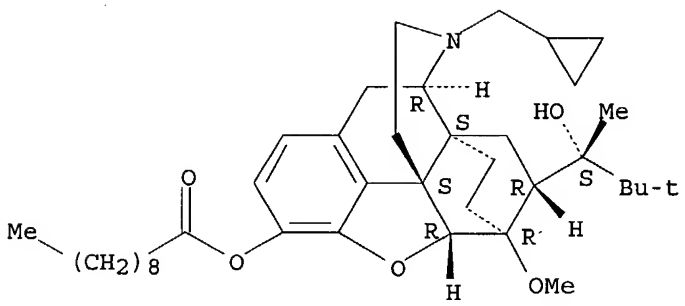
RN 171018-33-0 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-[(1-oxoheptyl)oxy]-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



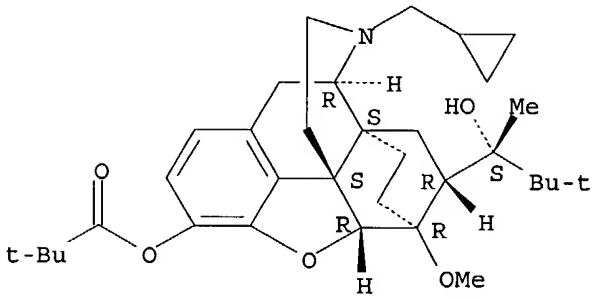
RN 693242-76-1 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-[(1-oxodecyl)oxy]-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



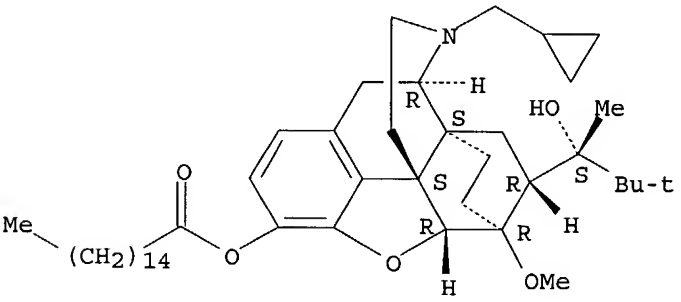
RN 693242-77-2 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-3-(2,2-dimethyl-1-oxopropoxy)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 693242-78-3 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-[(1-oxohexadecyl)oxy]-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

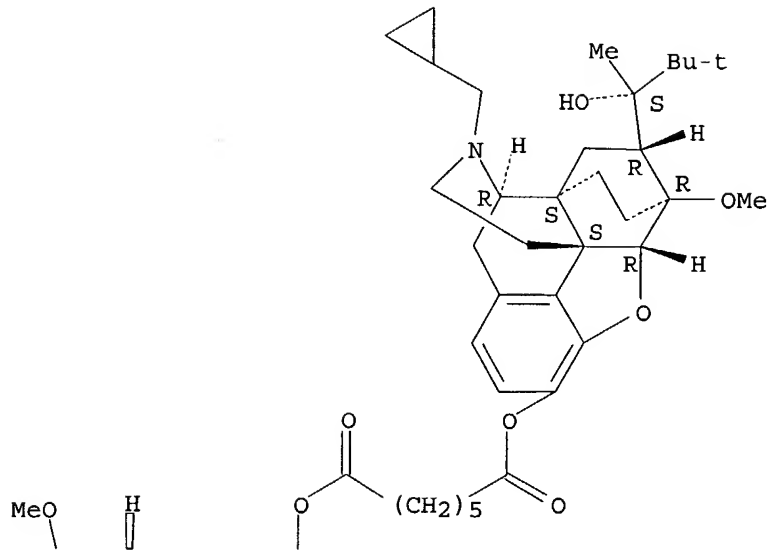
Absolute stereochemistry.



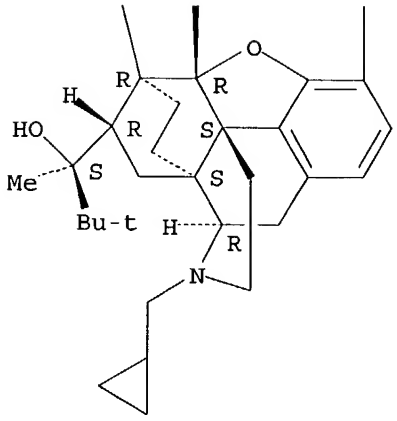
RN 693242-79-4 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 3,3'-[(1,7-dioxo-1,7-heptanediyl)bis(oxy)]bis[17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-, (αS,5α,7α)-(α'S,5'α,7'α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



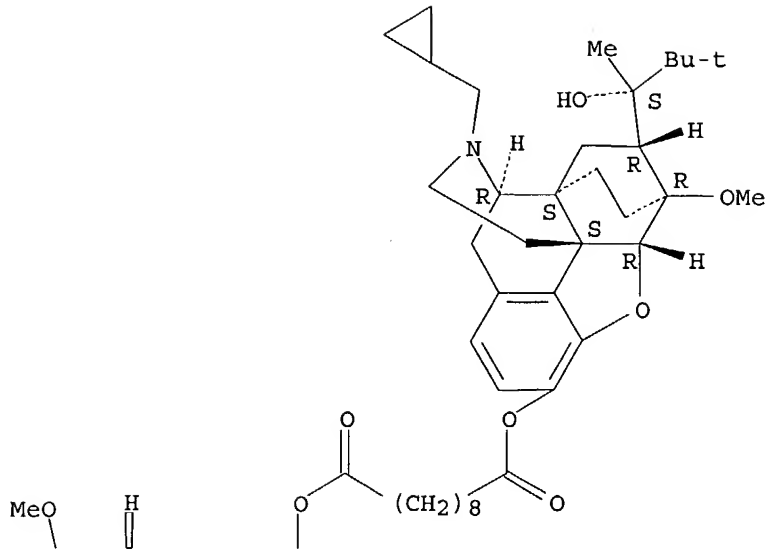
PAGE 2-A



RN 693242-80-7 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 3,3'-[(1,10-dioxo-1,10-decanediyl)bis(oxy)]bis[17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-, (αS,5α,7α)-(α'S,5'α,7'α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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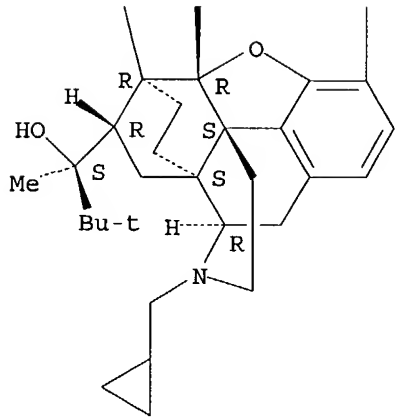
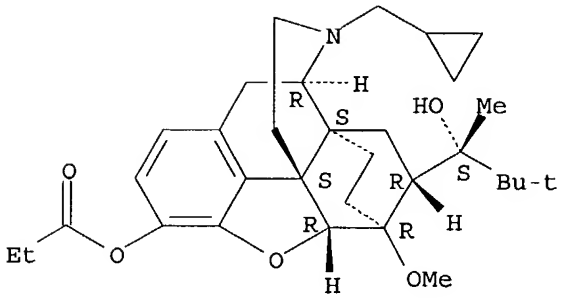


IT **171018-29-4**, Buprenorphine propionate **692729-06-9**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation and analgesic pharmaceutical composition of ester derivs. of buprenorphine)

RN 171018-29-4 CAPLUS

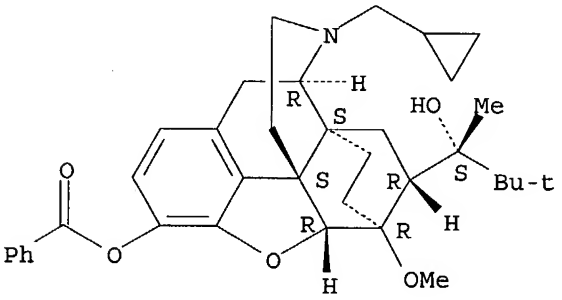
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-(1-oxopropoxy)-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 692729-06-9 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 3-(benzoyloxy)-17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN
AB An attempt to quant. describe human blood in vitro hydrolysis data for more than 80 compds. belonging to seven different noncongener series of ester-containing drugs is presented. A parameter not yet explored in pharmaceutical studies, the inaccessible solid angle Ωh, calculated around different atoms was used as a measure of steric hindrance, and the steric hindrance around the carbonyl sp2 oxygen (ΩhO=) proved the most relevant parameter. The obtained final equation, log t1/2 = -3.805 + 0.172ΩhO= - 10.146qC= + 0.112QLogP, also includes the AM1-calculated charge on the carbonyl carbon (qC=) and a calculated log octanol-water partition coefficient (QLogP) as parameters and accounts for 80% of the variability in the log half-lives of 67 compds. A number of structures are still mispredicted, but the equation agrees very well with a recently proposed mechanism for hydrolysis by carboxylesterases. The model, with a predictive power tested here on three unrelated structures, should be useful in estimating approx. rates of hydrolysis for prodrug or soft drug candidates ahead of their synthesis.

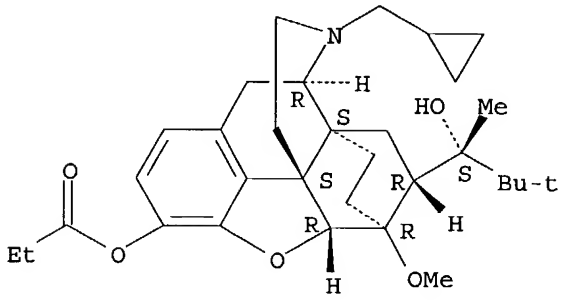
ACCESSION NUMBER: 1999:757495 CAPLUS
DOCUMENT NUMBER: 132:58723
TITLE: Quantitative Structure-Metabolism Relationships: Steric and Nonsteric Effects in the Enzymatic Hydrolysis of Noncongener Carboxylic Esters

AUTHOR(S): Buchwald, Peter; Bodor, Nicholas
CORPORATE SOURCE: Center for Drug Discovery, University of Florida Health Science Center, Gainesville, FL, 32610-0497, USA

SOURCE: Journal of Medicinal Chemistry (1999), 42(25), 5160-5168
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
LANGUAGE: English
IT **171018-29-4 171018-30-7 174586-17-5**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(steric and nonsteric effects in enzymic hydrolysis of noncongener carboxylic esters)
RN 171018-29-4 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-(1-oxopropoxy)-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 171018-30-7 CAPLUS
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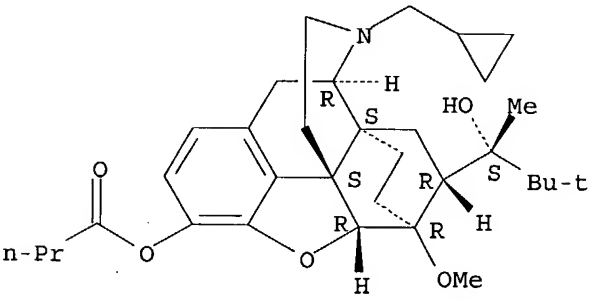
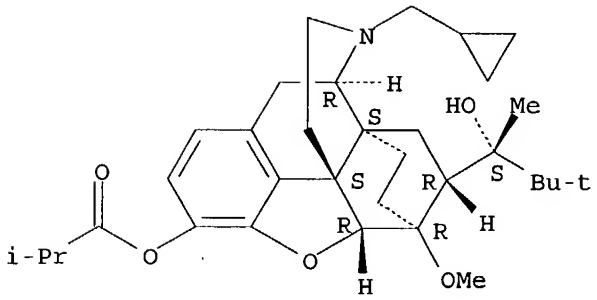
Absolute stereochemistry.



RN 174586-17-5 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-(2-methyl-1-oxopropoxy)-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 105 THERE ARE 105 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

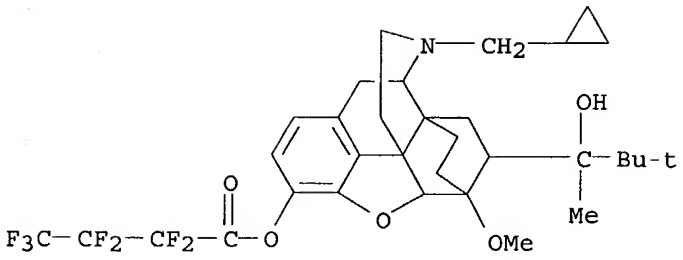
L4 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN

AB The authors describe a sensitive and specific method for the measurement of buprenorphine in human plasma. The method involves a structural analog as an internal calibrator, careful control of pH during sample extraction to maximize drug recovery, and back-extraction into acid followed by reextn. to eliminate endogenous interferences. After evaporation, sample residues are derivatized with heptafluorobutyric anhydride and analyzed by separation on a fused-silica polymethylsiloxane capillary column and electron-capture detection. Calibration curves were linear in the ranges 0.1-2.0 μg/L and 2.0-20 μg.L, with within-run CVs of 9.7% at 0.1 μg/L to 5.0% at 20 μg/L, and total CVs of 15.9% at 0.1 μg/L to 6.5% at 10 μg/L. The limit of quantification was 0.1 μg/L. The method was utilized in studies to determine the absolute bioavailability of sublingual doses of 2 mg of buprenorphine in 1 mL of 300 mL/L ethanol and the bioequivalence of sublingual 8-mg tablet and 300 mL/L ethanol solution formulations.

ACCESSION NUMBER: 1998:26558 CAPLUS
DOCUMENT NUMBER: 128:162492
TITLE: Subnanogram-concentration measurement of buprenorphine in human plasma by electron-capture capillary gas chromatography: application to pharmacokinetics of sublingual buprenorphine
AUTHOR(S): Everhart, E. Thomas; Cheung, Polly; Shwonek, Peter; Zabel, Karen; Tisdale, Eileen C.; Jacob, Peyton, III; Mendelson, John; Jones, Reese T.
CORPORATE SOURCE: Langley Porter Psychiatric Institute, University of California, San Francisco, CA, 94143-0984, USA
SOURCE: Clinical Chemistry (Washington, D. C.) (1997), 43(12), 2292-2302
CODEN: CLCHAU; ISSN: 0009-9147
PUBLISHER: American Association for Clinical Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **206013-23-2**
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative) (subnanogram-concentration measurement of buprenorphine in human plasma by electron-capture capillary gas chromatog. and application to pharmacokinetics of sublingual buprenorphine given in tablet and solution formulations)

RN 206013-23-2 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-3-(2,2,3,3,4,4,4-heptafluoro-1-oxobutoxy)-18,19-dihydro-6-methoxy-α-methyl-, (αS,5α,7α)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Buprenorphine I.HCl, useful as analgesic (no data), was prepared by acylation of compound II with cyclopropanecarbonyl chloride in the presence of Et3N in CHCl3 at 0-5° followed by reduction of the intermediate III with LiAlH4 in THF.

ACCESSION NUMBER: 1996:653389 CAPLUS
DOCUMENT NUMBER: 125:301302
TITLE: Method of manufacturing buprenorphine
INVENTOR(S): Stelmach, Piotr; Bobrowska, Ewa; Falek, Krzysztof
PATENT ASSIGNEE(S): Warszawskie Zaklady Farmaceutyczne Polfa, Pol.
SOURCE: Pol., 4 pp.
CODEN: POXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Polish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PL 166095	B1	19950331	PL 1991-289716	19910403
PRIORITY APPLN. INFO.:			PL 1991-289716	19910403

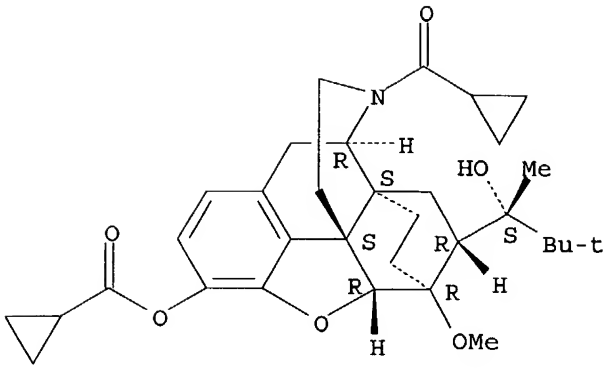
OTHER SOURCE(S): CASREACT 125:301302

IT **182693-14-7P**
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method of manufacturing buprenorphine)

RN 182693-14-7 CAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylcarbonyl)-3-[(cyclopropylcarbonyl)oxy]-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-, [5α,7α(S)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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AB Homologous 3-alkyl-ester prodrugs (C2 to C4) of buprenorphine with decreased crystallinity have been synthesized and evaluated for transdermal delivery commensurate with opioid dependence treatment. To assess the influence of derivatization on delivery, the permeation of the prodrugs through human skin was determined in vitro. Prodrug metabolism was measured in human blood and skin supernatant in vitro along with chemical hydrolysis controls. The prodrugs' octanol/water partition coeffs. were measured. Without exception, the prodrugs were completely hydrolyzed on passing through the skin and appeared as buprenorphine in the receptor compartment. However, using saturation conditions, in no instance did the buprenorphine flux through skin from a prodrug solution exceed the flux of buprenorphine base itself in vitro. Moreover, the flux of the acetyl ester, the least hydrophobic of the prodrugs, was not significantly elevated upon stripping the skin. Whether in blood or the skin supernatant, the prodrugs hydrolyzed in an apparent first-order fashion and rate consts. and half-lives were calculated We conclude from the results that the prodrugs' very high octanol/water partition coeffs. (hydrophobicity) placed them in viable tissue layer controlled diffusion. Moreover, the flux of the acetyl ester, the least hydrophobic of the prodrugs, was not significantly elevated upon stripping the skin. Whether in blood or the skin supernatant, the prodrugs hydrolyzed in an apparent first-order fashion and rate consts. and half-lives were calculated We conclude from the results that the prodrugs' very high octanol/water partition coeffs. (hydrophobicity) placed them in viable tissue layer controlled diffusion. Consequently, one does not derived the potential flux-increasing benefit of reducing crystallinity that was expected.

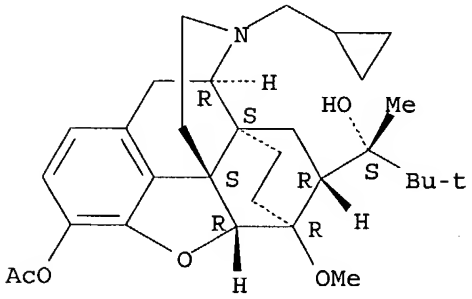
ACCESSION NUMBER: 1996:648717 CAPLUS
DOCUMENT NUMBER: 125:316126
TITLE: Permeation of buprenorphine and its 3-alkyl-ester prodrugs through human skin
AUTHOR(S): Stinchcomb, Audra L.; Paliwal, Anupam; Dua, Rajesh; Imoto, Hirofumi; Woodard, Ronald W.; Flynn, Gordon L.
CORPORATE SOURCE: College Pharmacy, University Michigan, Ann Arbor, MI, 48109, USA
SOURCE: Pharmaceutical Research (1996), 13(10), 1519-1523
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Plenum
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **171018-28-3 171018-29-4 171018-30-7 174586-17-5**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(permeation of buprenorphine and its 3-alkyl-ester prodrugs through human skin)

RN 171018-28-3 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 3-(acetyloxy)-17-(cyclopropylmethyl)-

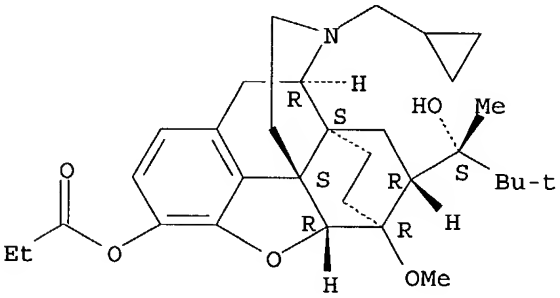
α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-, [5α,7α(S)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



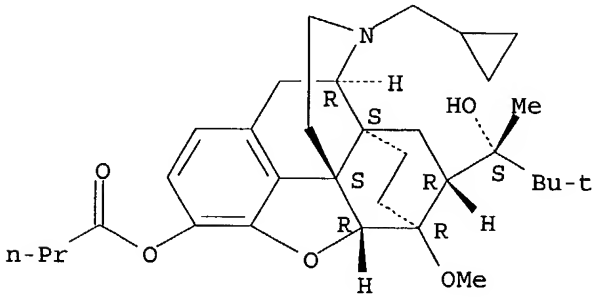
RN 171018-29-4 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-(1-oxopropoxy)-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



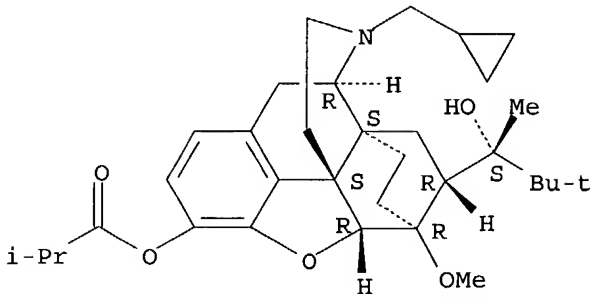
RN 171018-30-7 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-(1-oxobutoxy)-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 174586-17-5 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-(2-methyl-1-oxopropoxy)-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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AB In vitro skin permeation of buprenorphine (BUP) and three of its alkyl ester prodrugs was evaluated using hairless mouse skin. The 3 esters selected were the acetyl ester (Ac-BUP), Bu ester (Bu-BUP), and iso-Bu ester (Isb-BUP). These drugs were applied on the skin as saturated slurries in 3 vehicles commonly used to formulate agents for transdermal purposes: propylene glycol, polyethylene glycol 400 (PEG 400), and light mineral oil. Unique solubilities were found for each drug on each vehicle. Fluxes through hairless mouse skin were evaluated for each combination of drug and vehicle using Franz diffusion cells. From PEG 400 formulations, the skin fluxes of BUP, Ac-BUP, Bu-BUP, and Isb-BUP were 0.47, 1.64, 0.33, 0.75 μg/cm2/h, resp. Thus, among the 3 potential prodrugs chosen, only Ac-BUP showed significantly higher skin fluxes than BUP. There were no inter-vehicle differences in the fluxes from saturated slurries between the vehicles. Moreover, all the esters were detected substantially in the form of regenerated parent drug (BUP) in the receptor compartment. Indeed, only Ac-BUP exited the skin in a measurably intact form, but the fraction escaping metabolism in transit was small (approx. 2%). However, based on drug dispositions in the skin, the regeneration of buprenorphine seems to depend on the alkyl chain length of the ester moiety. The molar percentages of regenerated parent drug in whole drug collected from the skin following the permeation expts. were: Ac-BUP, 9.2%; Bu-BUP, 40.7%; Isb-BUP, 9.6%, resp. Thus, only Ac-BUP appears promising as a prodrug of buprenorphine, because it is not overly hydrophilic for skin permeation and is also highly metabolized to the parent compound while in the skin.

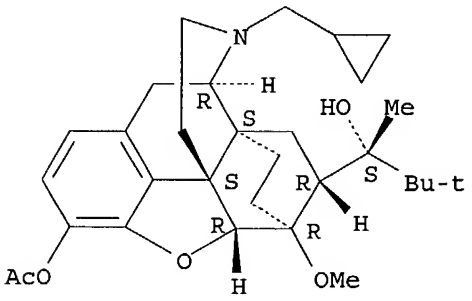
ACCESSION NUMBER: 1996:127303 CAPLUS
DOCUMENT NUMBER: 124:211800
TITLE: Transdermal prodrug concepts: permeation of buprenorphine and its alkyl esters through hairless mouse skin and influence of vehicles
AUTHOR(S): Imoto, Hirofumi; Zhou, ZiQi; Stinchcomb, Audra L.; Flynn, Gordon L.
CORPORATE SOURCE: Coll. Pharmacy, Univ. Michigan, Ann Arbor, MI, 48109-1065, USA
SOURCE: Biological & Pharmaceutical Bulletin (1996), 19(2), 263-7
CODEN: BPBLEO; ISSN: 0918-6158
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **171018-28-3**, Buprenorphine 3-acetate **171018-30-7**, Buprenorphine 3-butanoate **174586-17-5**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(vehicle effects on permeation of buprenorphine and its alkyl esters through skin)

RN 171018-28-3 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 3-(acetyloxy)-17-(cyclopropylmethyl)-

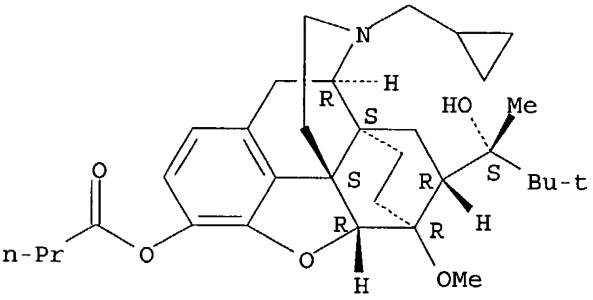
α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-, [5α,7α(S)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



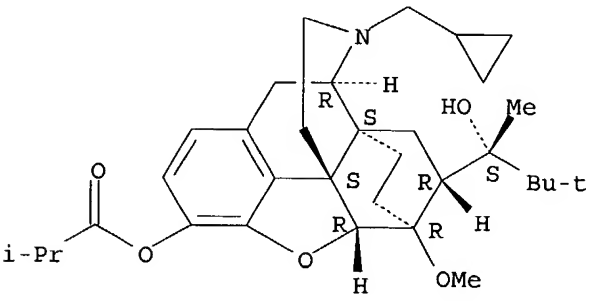
RN 171018-30-7 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-(1-oxobutoxy)-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 174586-17-5 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-(2-methyl-1-oxopropoxy)-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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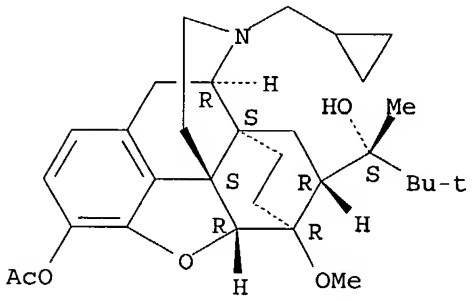
AB Modification of buprenorphine with an alkyl ester moiety accomplishes the physicochem. task required to improve its flux across a lipid membrane, as long as the diffusion coefficient of the drug has not been decreased and the

mol. mechanism of permeation remains the same. The ethers can be potential prodrugs for buprenorphine.

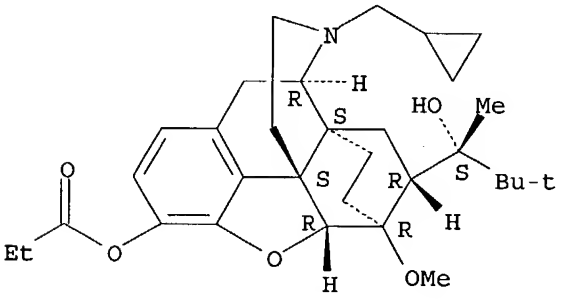
ACCESSION NUMBER: 1995:873901 CAPLUS
DOCUMENT NUMBER: 123:350075
TITLE: A solubility and related physicochemical property comparison of buprenorphine and its 3-alkyl esters
AUTHOR(S): Stinchcomb, Audra L.; Dua, Rajesh; Paliwal, Anupam; Woodard, Ronald W.; Flynn, Gordon L.
CORPORATE SOURCE: College of Pharmacy, The University of Michigan, Ann Arbor, MI, 48109-1065, USA
SOURCE: Pharmaceutical Research (1995), 12(10), 1526-9
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Plenum
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **171018-28-3 171018-29-4 171018-30-7**
171018-31-8 171018-32-9 171018-33-0
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solubility and related physicochem. properties of buprenorphine and its 3-alkyl esters)
RN 171018-28-3 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 3-(acetyloxy)-17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-, [5α,7α(S)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 171018-29-4 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-(1-oxopropoxy)-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

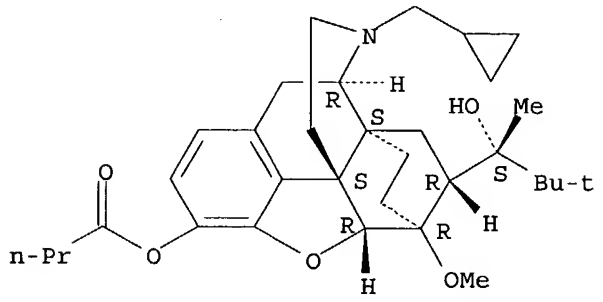
Absolute stereochemistry.



RN 171018-30-7 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-(1-

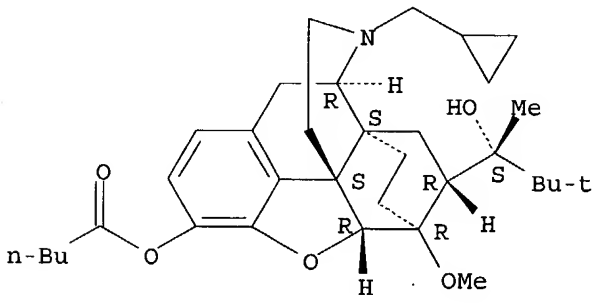
oxobutoxy)-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



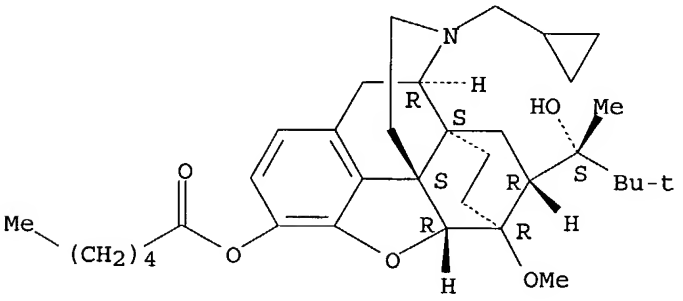
RN 171018-31-8 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-[(1-oxopentyl)oxy]-, [5α,7α(S)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



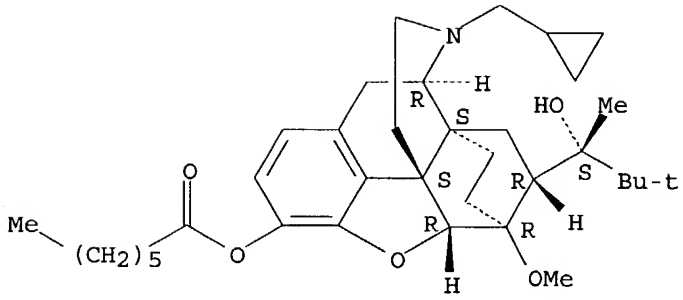
RN 171018-32-9 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-[(1-oxohexyl)oxy]-, [5α,7α(S)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 171018-33-0 CAPLUS
CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-[(1-oxoheptyl)oxy]-, (αS,5α,7α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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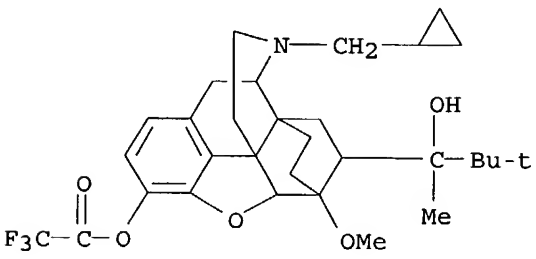
AB The mass spectra of 11 trifluoroacetyl (TFA) derivs. of opioid bases were recorded quasi-simultaneously by pos. electron impact mass spectrometry and neg. chemical ionization mass spectrometry at low reagent gas pressure (electron attachment, reagent gas CH4 at 3 + 10-3 torr). The derivatization was accomplished either by injecting the free base together with N-methyl-bis-trifluoroacetamide directly in the gas chromatog. (GC), or by preheating the free base together with MBTFA at 220°. All TFA derivs. except for the hydromorphone, naloxone and apomorphine derivative yielded m/z 113, the CF3COO- residue, as base anion. With hydromorphone and naloxone, 2 and 3 TFA groups resp. were introduced into the mol. For all derivs., the neg. total ion current (TIC) was stronger than the pos. TIC. The derivs. showed better chromatog. properties than the parent compds. The detection levels of derivs. determined by GC with electron capture detector and GC with neg. ion detection were similar. Morphine [57-27-2] in urine of a drug addict was identified by using the proposed method.

ACCESSION NUMBER: 1985:608220 CAPLUS
DOCUMENT NUMBER: 103:208220
TITLE: Dual mass spectrometry of trifluoroacetyl derivatives of opioid bases
AUTHOR(S): Yashiki, Mikio; West, Fanny B.; Brandenberger, Hans
CORPORATE SOURCE: Sch. Med., Hiroshima Univ., Hiroshima, 734, Japan
SOURCE: GC-MS News (1985), 13(4), 101-6
CODEN: GMNEDS; ISSN: 0388-1288
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **99318-72-6**
RL: PRP (Properties)
(mass spectra of)

RN 99318-72-6 CAPLUS

CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-6-methoxy-α-methyl-3-[(trifluoroacetyl)oxy]-, [5α,7α(S)]- (9CI) (CA INDEX NAME)



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